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ORIGINAL INVESTIGATION

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18-Methoxycoronaridine attenuates nicotine-induced dopamine release and nicotine preferences in rats

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Abstract Two studies were conducted to assess, in vivo, potential anti-nicotinic effects of the *iboga* alkaloid ibogaine and its synthetic congener 18-methoxycoronaridine (18-MC). As previously demonstrated for ibogaine, using microdialysis, pretreatment (19 h beforehand) with 18-MC (40 mg/kg, IP) significantly attenuated nicotine-induced dopamine release in the nucleus accumbens of awake and freely moving rats. In an oral model of nicotine self-administration, both ibogaine and 18-MC decreased rats' preferences for nicotine for at least 24 h. Acutely, during the first hour after administration, ibogaine depressed responding for water as well as for nicotine; however, during this same time, 18-MC reduced nicotine intake without affecting responding for water. The results suggest that 18-MC might be the prototype of a new treatment for smoking.

Key words Nicotine · Ibogaine · 18-Methoxycoronaridine · In vivo microdialysis · Drug self-administration · Smoking

Introduction

Ibogaine, an alkaloid found in *Tabernanthe iboga*, is claimed (H. Lotsof, US patents: numbers 4, 449, 096; 4, 587, 243; 4, 857, 523; 5, 026, 697; 5, 124, 994) to be effective in interrupting dependence on opioids, stimulants, alcohol and nicotine (smoking). While preclinical studies in rats have found it to decrease morphine (Glick et al. 1991), cocaine (Cappendijk and Dzoljic

1993; Glick et al. 1994), and alcohol (Rezvani et al. 1995) self-administration, only neurochemical interactions of ibogaine with nicotine have been reported. Ibogaine blocks nicotine-induced dopamine release in the nucleus accumbens (Benwell et al. 1996; Maisonneuve et al. 1997), similar to its effect on dopamine release induced by morphine (Maisonneuve et al. 1991). 18-Methoxycoronaridine (18-MC), a novel *iboga* alkaloid congener, has effects that mimic those of ibogaine on morphine and cocaine self-administration (Glick et al. 1996a) and on alcohol intake (Rezvani et al. 1997); however, 18-MC does not produce the typical side effects (e.g., tremor, decreased motivated behavior in general) and toxicity (cerebellar Purkinje cell loss) associated with ibogaine (cf. Molinari et al. 1996). In the present study, we have first determined if 18-MC, like ibogaine, blocks nicotine-induced dopamine release in the nucleus accumbens. Subsequently, using a recently developed oral model of nicotine self-administration (Glick et al. 1996c), we have compared ibogaine and 18-MC in terms of their effects on rats' preferences for nicotine.

Materials and methods

Subjects

Subjects were male Sprague-Dawley (Taconic, Germantown, N.Y., USA) and female Long-Evans (Charles River, Kingston, N.Y., USA) rats approximately 3 months old and weighing 250–300 g and 230–250 g, respectively, at the beginning of the studies. Rats were maintained on a normal light/dark cycle (lights on/off at 7:00 a.m./7:00 p.m.). For all animal experiments the "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed.

Drugs

Nicotine hydrogen bitartrate and ibogaine hydrochloride were purchased from the Sigma Chemical Company (St Louis, Mo., USA).

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Racemic 18-MC hydrochloride was synthesized by Martin Kuehne and Upul Bandarage, University of Vermont, Burlington, VT (cf. Glick et al. 1996). Ibogaine and 18-MC were dissolved in sterile water and phosphate buffer, respectively, at a concentration of 10 mg/ml (ibogaine) or 20 mg/ml (18-MC). For IV administration, used in the microdialysis experiment, nicotine (0.32 mg/kg, free base) was dissolved in saline; the pH of the nicotine solution was adjusted to 7.0 with a small amount of 10 M NaOH. For the oral self-administration experiment, an aqueous solution of the nicotine salt was made at a concentration of 4 µg/ml (1.4 µg/ml of the base); the solution was adjusted to a pH of 7.0.

In vivo microdialysis

Under pentobarbital anesthesia (50 mg/kg, IP), male Sprague-Dawley rats had their external jugular vein catheterized with a polyethylene-silicone catheter and one guide cannula was implanted stereotactically over the nucleus accumbens. The coordinates were chosen such that, when inserted, the tips of the dialysis probes were located in the medial portion of the shell area of the nucleus accumbens: AP, +1.6 mm and L, ± 0.7 mm with respect to bregma, V, -8.6 mm from the surface of the skull (Paxinos and Watson 1986). The animals were allowed to recover from surgery for 4 days.

Similar to the procedure used in our previous study with ibogaine (Maisonneuve et al. 1997), rats were pretreated with 18-MC (40 mg/kg, IP) or saline (control) 19 h prior to infusion of nicotine. The night before the dialysis experiment, the rat was placed in a chamber with free access to food and water. With the rat briefly anesthetized with Brevital (0.05 ml IV), a dialysis probe (Carnegie Medicin probes: 2 mm) was inserted through the guide cannula. Artificial CSF containing 146 mM NaCl, 2.7 mM KCl, 1.2 mM CaCl₂ and 1.0 mM MgCl₂ was delivered by a Harvard syringe pump at a flow rate of 1 µl/min. Collection of perfusate began the next day. Fifteen-minute fractions were collected in vials containing 1.5 µl of 1.1 M perchloric acid solution (containing 50 mg/l EDTA and 50 mg/l sodium metabisulfite). Before the end of the sixth baseline sample, the catheter was primed (25 µl in 2 min). At the beginning of the seventh sampling period, the rat received a 5-min IV infusion of nicotine (0.32 mg/kg per infusion, free base). The collection of dialysate samples was stopped 1 h after the infusion. Upon completion of an experiment, the catheter's functional status was assessed by IV injection of 0.05 ml Brevital. The rats were then killed by an overdose of pentobarbital. Brains were removed and frozen, and 50 µm coronal sections were sliced in a cryostat. The tracks left by the probes were identified and their exact positions determined by reference to the Paxinos and Watson atlas (1986). Strict criteria were applied to determine whether the locations of the probes were acceptable or not: the tracks were not to be visible at the bottom of the brain, and had to be within a third of the distance separating two easily recognizable landmarks—the midline and the anterior commissure. Only the dialysates of animals whose tracks were in the correct locations were analyzed.

Dialysate samples were assayed for dopamine by HPLC with electrochemical detection. The HPLC system consisted of a Waters 712 Wisp autosampler, a Waters 510 solvent delivery system, a Spherisorb C18 column and a Waters 464 electrochemical detector with a working electrode set at a potential of 0.79 V with respect to a silver-silver chloride reference electrode. The mobile phase consisting of 6.9 g/l sodium monobasic phosphate, 500–560 mg/l heptane sulfonic acid, 100 mg/l disodium EDTA and 120 ml/l methanol, was adjusted with HCl to pH 3.6 and was pumped at a rate of 1.2 ml/min. Chromatograms were integrated, compared to standards and analyzed using Hewlett Packard ChemStation software.

Oral nicotine self-administration

All testing was conducted in Coulbourn Instruments operant cages, each enclosed in a sound-attenuated cubicle. Responses on either

of two levers mounted on the front wall of each test cage were recorded on an IBM compatible 486 computer with a Med Associates, Inc. interface. Two fluid delivery systems, each consisting of a fluid container connected to a solenoid, delivered 0.1 ml nicotine solution or water to stainless steel drinking cups located above each lever.

Rats were initially placed into the operant chambers overnight and trained to respond for water, using both levers, on a continuous reinforcement schedule. Following nocturnal training, rats were switched to 1-h sessions during the day, 5 days a week (Monday-Friday), and maintained on a 23-h water deprivation schedule. Rats were provided ad libitum access to water after test sessions on Fridays, with the water deprivation schedule reinstated on Sundays in preparation for Mondays' test sessions. After five consecutive daily sessions in which rats made at least 50 responses/h, nicotine was introduced. The concentration was 4 µg/ml. Rats received nicotine by pressing one lever and water by pressing the other. Side of presentation of nicotine was alternated each day. When rates of responding and nicotine preferences (responses for nicotine as a percentage of total responses) were stable, varying no more than ±10% from day to day, rats were administered IP (15 min before testing) various doses of ibogaine (10–40 mg/kg), (18-MC (10–40 mg/kg) or saline (0 mg/kg) on Wednesdays, with at least 7 days intervening between successive treatments; to preclude any carry-over effects of the highest doses (cf. Glick et al. 1991, 1996a), doses were administered in ascending order and five or six rats were tested at each dose (different groups of rats were used for testing the effects of ibogaine and 18-MC). Only rats having preferences for nicotine (i.e., consistently making more responses for nicotine than for water on at least 10 consecutive days) were used to assess the effects of ibogaine and 18-MC (i.e., not all rats have nicotine preferences, cf. Glick et al. 1996c; approximately 50% of the rats screened for this study had nicotine preferences).

The current procedure of maintaining rats on a Monday-Friday 23-h water deprivation schedule, with daily 1-h operant test sessions (water reward), has been used in this laboratory for several years (e.g., Glick et al. 1996c). As previously found, such rats exhibit small and gradual increases in body weight consistent with the asymptotic growth curves of normal female rats. It is important to note that, in the present study, the total fluid intake of nicotine self-administering rats was at least as much as when water alone was self-administered.

Statistical analysis

The software package Statistica (StatSoft, Inc., Tulsa, Ok., USA) was utilized for statistical analysis of all data. Both *in vivo* microdialysis and nicotine self-administration data were analyzed using analysis of variance (ANOVA) with repeated measures followed by Newman-Keuls tests for post-hoc comparisons.

Results

Effects of 18-MC on basal extracellular levels of dopamine, DOPAC and HVA and on nicotine-induced dopamine changes

Two-way ANOVAs with repeated measures showed that basal levels of dopamine, dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) did not differ between the 18-MC and saline groups. For both groups pooled, these extracellular levels were in picomol/10 µl ± SEM for dopamine, 0.0183 ± 0.0002, for DOPAC, 11.667 ± 0.132, for HVA, 5.113 ± 0.076.

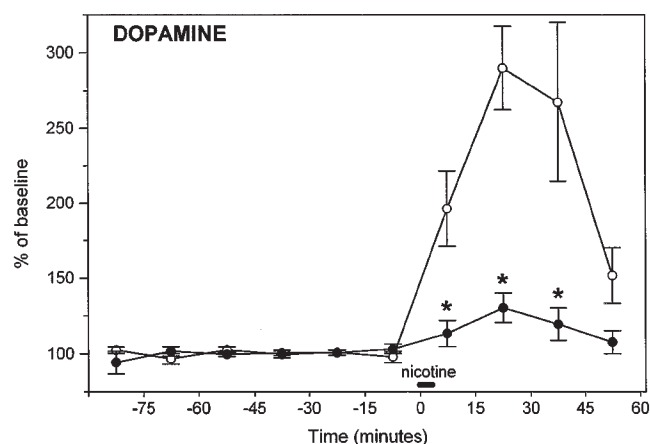


Fig. 1 Effects of 18-MC (●), 40 mg/kg ($n = 7$), administered 19 h prior to a nicotine infusion (0.32 mg/kg per infusion), on extracellular levels (% of baseline; mean $\pm$ SEM) of dopamine in the nucleus accumbens; an asterisk indicates significant ($P < 0.05$) differences from saline (○) ($n = 5$)

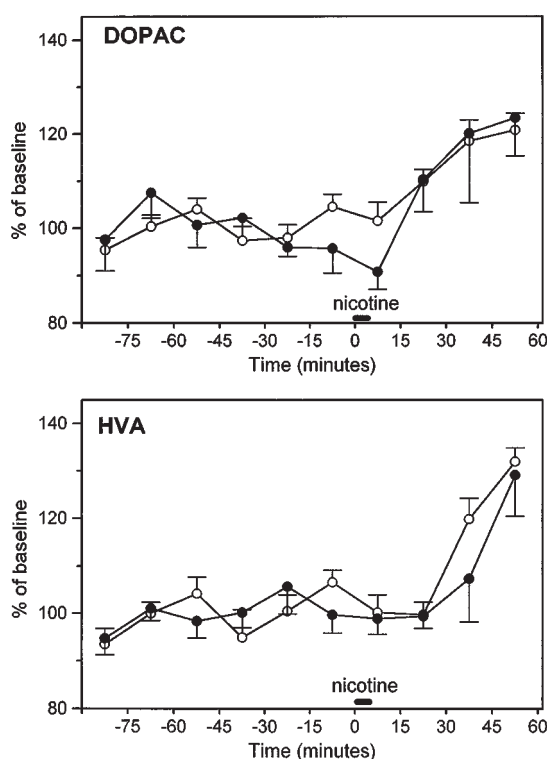


Fig. 2 Effects of 18-MC (●), 40 mg/kg ($n = 7$), administered 19 h prior to a nicotine infusion (0.32 mg/kg per infusion), on extracellular levels (% of baseline; mean $\pm$ SEM) of DOPAC and HVA in the nucleus accumbens. ○ Saline

A two-way ANOVA with repeated measures revealed that 18-MC pretreatment significantly attenuated the increase in extracellular dopamine levels induced by nicotine [treatment $\times$ time interaction, $F(3,30) = 3.94$, $P < 0.02$; Newman-Keuls tests: $P < 0.05$; Fig. 1]. 18-MC did not significantly alter the increases in

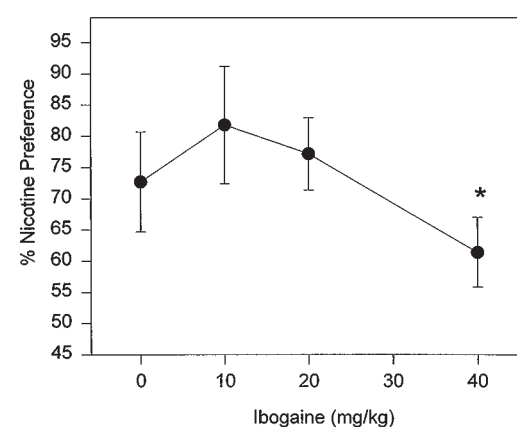
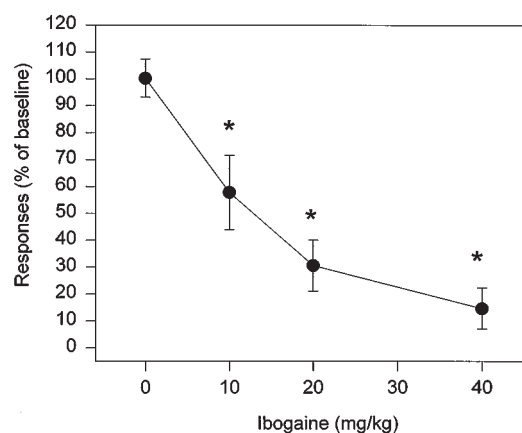


Fig. 3 Effects of ibogaine ($n = 5-6$ /dose), administered 15 min before a 1-h test session, on total responses (% of baseline; mean $\pm$ SEM) and % nicotine preferences (mean $\pm$ SEM) of rats self-administering nicotine; an asterisk indicates significant ($P < 0.05-0.001$) differences from 0 dose (saline)

dopamine metabolites produced by nicotine (Fig. 2). These effects of 18-MC were very similar to those previously observed with ibogaine (Maisonneuve et al. 1997).

Effects of ibogaine and 18-MC on operant response rates and on nicotine preferences

On the day of administration (day 1), all doses (10–40 mg/kg) of ibogaine significantly decreased total (i.e., water plus nicotine; Fig. 3, top) rates of responding [ANOVA: $F(3,15) = 15.18$, $P < 0.0001$; Newman-Keuls tests: $P < 0.05-0.001$] as well as separate (Fig. 5, top) rates of responding for nicotine [ANOVA: $F(3,15) = 12.11$, $P < 0.0003$; Newman-Keuls tests: $P < 0.05-0.001$] and water [ANOVA: $F(3,15) = 10.82$, $P < 0.0005$; Newman-Keuls tests: $P < 0.05-0.001$]. Only the highest dose, 40 mg/kg, significantly decreased nicotine preferences on day 1 [Fig. 3, bottom; ANOVA: $F(3,15) = 5.58$, $P < 0.01$; Newman-Keuls test: $P < 0.05$; also cf. Fig. 5, top], and this same dose abolished nicotine preferences on the following day [Fig. 6,

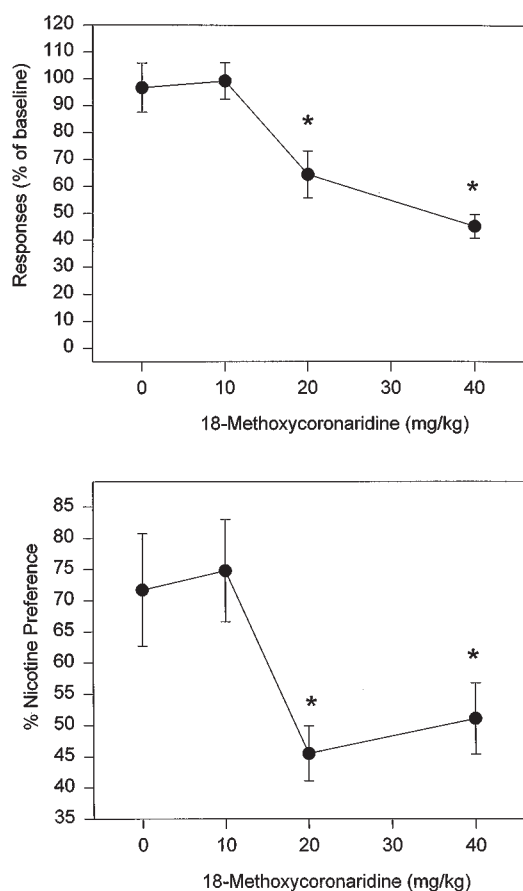


Fig. 4 Effects of 18-MC ($n = 6/\text{dose}$), administered 15 min before a 1-h test session, on total responses (% of baseline; mean $\pm$ SEM) and % nicotine preferences (mean $\pm$ SEM) of rats self-administering nicotine; an asterisk indicates significant ($P < 0.05\text{--}0.01$) differences from 0 dose (saline)

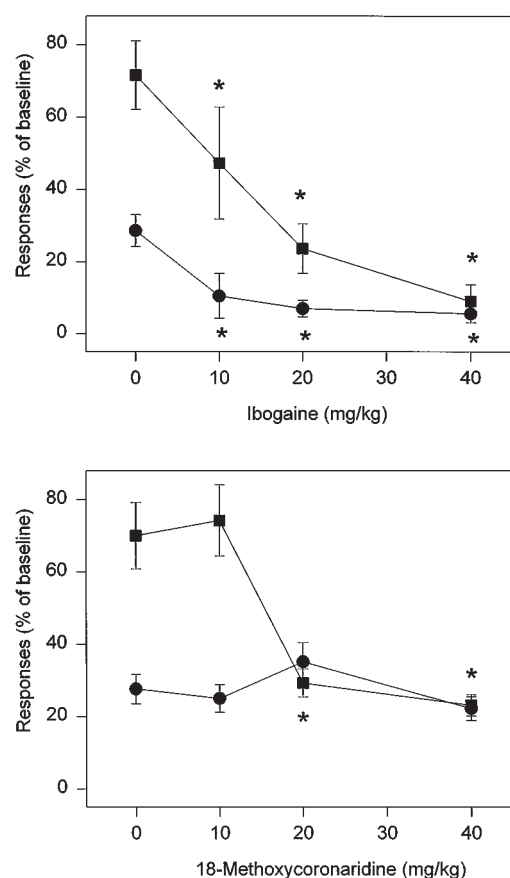


Fig. 5 Effects of ibogaine ($n = 5\text{--}6/\text{dose}$), and 18-MC ($n = 6/\text{dose}$), administered 15 min before a 1-h test session, on separate response rates (% of baseline total; mean $\pm$ SEM) for nicotine (■) and water (●); an asterisk indicates significant ($P < 0.05\text{--}0.001$) differences from 0 dose (saline)

bottom; ANOVA: $F(4,20) = 7.24$, $P < 0.001$; Newman-Keuls test: day 2 versus baseline, $P < 0.01$]. Neither 10 nor 20 mg/kg significantly affected nicotine preferences on any day. There was no effect of ibogaine on total response rates (Fig. 6, top) on any day after day 1.

On the day of administration, the two highest doses (20 and 40 mg/kg) of 18-MC significantly decreased total rates of responding [ANOVA: $F(3,15) = 8.84$, $P < 0.002$; Newman-Keuls tests: $P < 0.05\text{--}0.01$; Fig. 4, top]. When responding for nicotine and water was analyzed separately, both 20 and 40 mg/kg significantly decreased responding for nicotine [ANOVA: $F(3,15) = 10.80$, $P < 0.0005$; Newman-Keuls tests: $P < 0.005\text{--}0.002$; Fig. 5, bottom) but neither dose of 18-MC significantly affected responding for water. Both 20 and 40 mg/kg 18-MC abolished nicotine preferences on the day of administration [Fig. 4, bottom; ANOVA: $F(3,15) = 7.03$, $P < 0.004$; Newman-Keuls tests: $P < 0.01$; also cf. Fig. 5, bottom], and the higher dose continued to do so on the day after administration [Fig. 7, bottom; ANOVA: $F(4,20) = 8.02$, $P < 0.001$; Newman-Keuls test: day 2 versus baseline, $P < 0.01$]. There was

no effect of 18-MC on total response rates (Fig. 7, top) on any day after day 1.

Discussion

Substantial evidence has indicated that the reinforcing effect of nicotine is mediated by the dopaminergic mesolimbic system having cell bodies in the ventral tegmental area and terminals in the nucleus accumbens. Acute administration of nicotine to rats has been reported to increase the firing rate of dopamine neurons (Grenhoff et al. 1986), increase dopamine synthesis (Carr et al. 1989), and increase dopamine release (Imperato et al. 1986). Dopamine receptor antagonists and 6OHDA lesions of the mesolimbic pathway have been found to decrease intravenous self-administration of nicotine in rats (Corrigall and Coen 1991; Corrigall et al. 1992). In the present study, in accordance with previous data from other laboratories (e.g., Imperato et al. 1986; Damsma et al. 1989; Brazell et al. 1990; Benwell et al. 1996) as well as from this laboratory

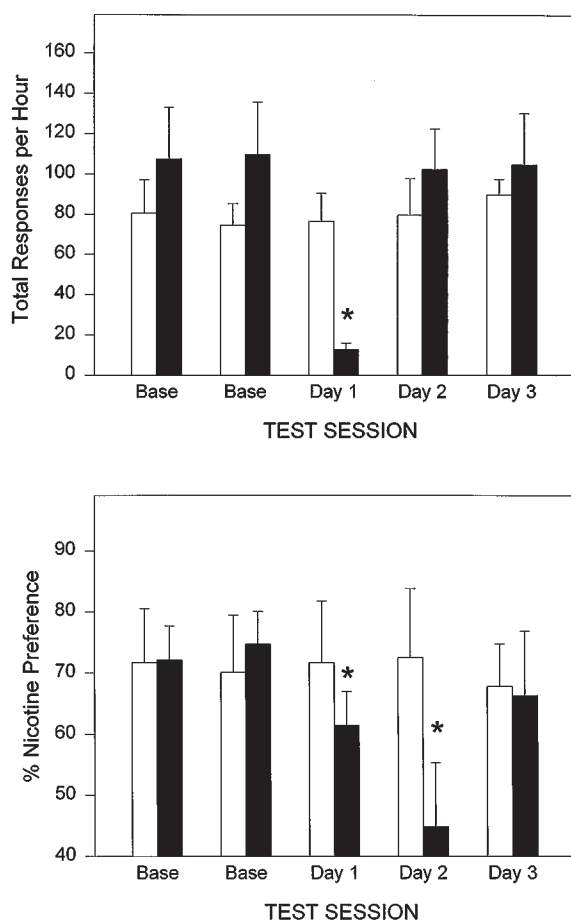


Fig. 6 Aftereffects of ibogaine, 40 mg/kg ($n = 6$), on total responses (mean $\pm$ SEM) and % nicotine preferences (mean $\pm$ SEM) of rats self-administering nicotine; an asterisk indicates significant ($P < 0.05$ – 0.01) differences from baseline. Ibogaine ■ or saline □ was administered once, 15 min before the beginning of testing on day 1

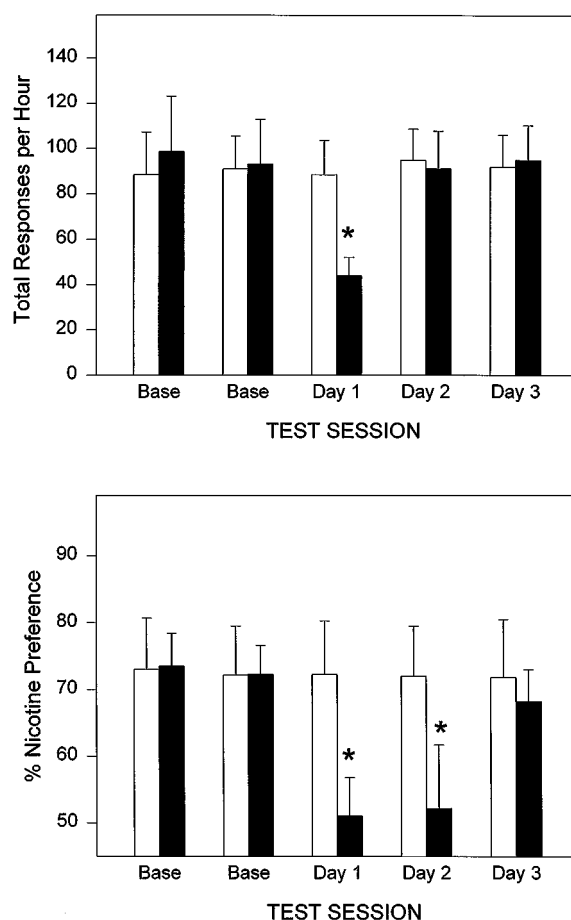


Fig. 7 Aftereffects of 18-MC, 40 mg/kg ($n = 6$), on total responses (mean $\pm$ SEM) and % nicotine preferences (mean $\pm$ SEM) of rats self-administering nicotine; an asterisk indicates significant ($P < 0.01$) differences from baseline. 18-MC ■ or saline □ was administered once, 15 min before the beginning of testing on day 1

(Maisonneuve et al. 1997), an acute IV infusion of nicotine elicited a robust increase in extracellular levels of dopamine in the nucleus accumbens. Pretreatment (19 h beforehand) with 18-MC, as previously shown for ibogaine (Maisonneuve et al. 1997), largely attenuated the nicotine-induced increase in extracellular dopamine levels. The data suggested that 18-MC, as well as ibogaine, might suppress nicotine self-administration.

An oral self-administration model of nicotine preference in rats was initially developed to circumvent some of the controversy concerning the reinforcing efficacy of nicotine administered via the intravenous route (cf. Glick et al. 1996c). Although that controversy seems to be disappearing, in view of several additional reports of IV nicotine self-administration in rats (e.g., Shaham et al. 1997; Shoaib et al. 1997; Valentine et al. 1997), the oral model has nevertheless shown promise of becoming quite useful in assessing potential treatments for smoking. Both ibogaine and 18-MC decreased rats' preferences for nicotine. On the day of administration (day 1) both drugs also decreased total

rates of responding; however, as shown in Fig. 4, whereas ibogaine significantly affected responding for water as well as for nicotine, 18-MC decreased responding for nicotine without altering responding for water. This selectivity of 18-MC was reminiscent of that previously demonstrated in our study of the effects of 18-MC on morphine and cocaine self-administration (Glick et al. 1996a).

Preferences for nicotine were still markedly attenuated a day after administration (day 2) of 40 mg/kg of either ibogaine or 18-MC. In both cases, this occurred even though total response rates had returned to normal; that is, apparently to maintain normal fluid intake, responding for water increased to compensate for the decrease in responding for nicotine. The basis for the prolonged effects of ibogaine on nicotine preferences (24–25 h), as well as on nicotine-induced dopamine release (19–20 h), is not entirely understood, but some reasonable inferences can be made. Although ibogaine has an active metabolite, noribogaine (Mash et al. 1995; Pearl et al. 1995), and the pharmacology of

noribogaine is similar to that of ibogaine (Glick et al. 1996b), it is not clear, at least in rats (Pearl et al. 1997), if noribogaine persists in the body in high enough concentrations to mediate effects of ibogaine a day after its administration. However, it has been shown that ibogaine is sequestered in fat (Hough et al. 1996), and it is possible that this creates a depot-like preparation in which ibogaine is slowly released over a long time period. Ibogaine, as well as noribogaine, have been screened in many receptor systems (e.g., Deecher et al. 1992; Sweetnam et al. 1995; Staley et al. 1996), and it appears that, of all the sites examined, the cholinergic nicotinic receptor is the site that binds ibogaine with the highest affinity (ibogaine appears to be a noncompetitive blocker, cf. Badio et al. 1997). Thus it is possible that low brain levels of ibogaine, a day after its administration (Pearl et al. 1997), may be sufficient to block nicotinic receptors and reduce rats' responses to nicotine. Very little information regarding the distribution and metabolism of 18-MC is available, so it is not yet possible to conclude whether a similar mechanism is likely to be involved in mediating the prolonged effects of 18-MC. Similarly, less is known about which molecular targets 18-MC might potentially interact with, although preliminary studies in this laboratory suggest that it has a narrower spectrum of action than ibogaine. For example, both ibogaine (Maisonneuve et al. 1991) and 18-MC (Glick et al. 1996a) acutely (first 3 h) decrease extracellular levels of dopamine in the nucleus accumbens and striatum. Acutely, ibogaine also increases extracellular serotonin levels in these brain regions (Mash et al. 1995; Wei et al. 1997), but 18-MC does not have this effect (Wei et al. 1997).

In summary, 18-MC pretreatment (19 h), as previously demonstrated for ibogaine, attenuated nicotine-induced release of dopamine in the nucleus accumbens of awake and freely moving rats. In an oral self-administration paradigm, both ibogaine and 18-MC reduced or abolished rats' preferences for nicotine for at least 24 h. While the initial effect of ibogaine on the day of administration was confounded by nonspecific depression of responding, 18-MC selectively reduced nicotine self-administration without altering responding for water. 18-MC warrants further study as the prototype of a novel treatment for smoking.

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